32. (New) The nucleic acid of claim 31, wherein the encoded mosaic protein comprises the amino acid sequences set forth in SEQ ID NOs:23-33.

33. (New) The nucleic acid of claim 31, wherein the encoded mosaic protein comprises the amino acid sequences set forth in SEQ ID NOs:23-33 in numerical order.

DH

34. (New) A nucleic acid encoding a mosaic protein comprising more than two homologous antigenic peptides from different genotypes or subtypes of a species, wherein the encoded mosaic protein has an amino acid sequence set forth in SEQ ID NO:52.

REMARKS

Claims 1-13 and 16-30 are pending in this application. New claims 31-34 are added herein. Claims 1-12 and 20-30 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 13 and 16-19 are currently under examination. Claims 17 and 19 remain objected to for their dependence from rejected claims. Claims 13, 16 and 18 remain rejected. Claims 17 and 19 have been amended to overcome the current objection. As required by 37 C.F.R. § 1.121, a marked-up version of the amended claims is attached hereto. New claims 31-34 have been added to more clearly and precisely claim the present invention. Support for these claims can be found in the specification as filed. Support for the amendments

and new claims can be found in the currently pending claims and throughout the specification as indicated below.

Applicants gratefully acknowledge Examiner's citation of references previously submitted as Exhibits in response to the Office Action of April 4, 2002, thereby making those cited references of record in the present case.

Applicants also acknowledge the withdrawal of the prior objection to the specification upon entry of the prior amendment to the specification such that the trade name MATRIX is now accompanied by the generic descriptor "immunoassay."

In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

Applicants respectfully request that the Patent Office update its records to reflect applicants' attorney docket number, which is included on this document.

I. Rejection under 35 U.S.C. § 112, first paragraph

Claims 13, 16 and 18 are rejected under 35 U.S.C. § 112, first paragraph, as being allegedly being drawn to subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, it is alleged that "the specification nowhere indicates that applicant considers the invention to include proteins wherein the epitopes from the same domain are not homologous to one another." Thus, it is

alleged that the specification, which is acknowledged by the Examiner to describe a mosaic protein "comprising a plurality of homologous antigenic peptides from different genotypes of hepatitis virus," does not support any claim lacking a specific limitation that the antigenic peptides be homologous peptides. Even though Applicants do not concede that the Examiner's characterization is correct, as the present amendment to claims 13, 17 and 19 and new claims 31 and 34 each incorporate specific recitation that the claimed nucleic acids encode sequence of homologous peptides, Applicants submit the present basis of rejection is overcome for claims 13, and 16-19 and is inapplicable to newly added claims 31-34. Applicants therefore respectfully request removal of this basis of rejection.

II. Rejection under 35 U.S.C. § 112, second paragraph

Claims 13 and depend claims 16 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter the Applicants regard as the invention. Specifically, the claims are characterized as describing "a nucleic acid encoding a multiple epitope fusion protein...comprising more than two antigenic peptides from the same domain from different genotypes of hepatitis C virus," while the specification is alleged to describe a "mosaic protein comprising a plurality of homologous antigenic peptides from different genotypes of a hepatitis virus." While Applicants do not agree that the invention as claimed is indefinite, Applicants submit that the present amendment of the claims to recite *inter alia* "...more than two

homologous antigenic epitopes..." renders this basis of rejection moot. Accordingly, Applicants request that the Examiner remove of this basis of rejection from claims 13, and 16-19 and further that this basis of rejection not be applied to new claims 31-34.

III. Rejections under 35 U.S.C. § 102

Claims 13 and 16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Yagi et al. Specifically, the claimed nucleic acids "read on a nucleic acid encoding a protein comprising more than two antigenic peptides from the same domains from different genotypes of HCV." Yagi et al. is characterized by the Examiner as teaching a chimeric HCV antigenic protein that "includes 9 selected epitope regions, including two from NS3, and two from two different genotypes of NS4" and from this it is concluded that when the present pending claims are given one possible claim interpretation, namely that the antigenic peptides need not be homologous, the proteins and nucleic acids taught by Yagi et al. anticipate the claims. In response, Applicants submit that the amendment of the present claims to include the recitation of homologous antigenic epitopes removes the ambiguity referred to by the Examiner that allowed for the claim interpretation in which the proteins of Yagi et al. anticipated the present claims. Accordingly, Applicants request removal of this basis of rejection and allowance of all pending claims, including the newly added claims 31-34 which also include this limitation to homologous antigenic epitopes.

IV. Rejections under 35 U.S.C. § 103

A. The rejection of claims 13, 16 and 18 under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Khudyakov et al., in view of Zhang et al., Bukh et al. and Chien et al. was maintained. Amendment of claim 13 in the last response (Amendment C) to recite "comprising more than two antigenic peptides" is not considered to overcome the prior rejection. Applicants submit, however, that the present amendment to recite homologous antigenic peptides does distinguish the presently pending claims from any teachings of the cited art. Specifically, while the Examiner maintained that the earlier pending claims not including specific recitation of homologous antigenic epitopes were within the teaching of the Khudyakov reference on page 7073, left column ("...in discussing the mosaic peptide taught in the reference, the paper states 'such a design allows for the introduction of additional antigenic regions'..."), each of the claims as presently amended or added do require the inclusion of homologous antigenic epitopes. This, Applicants submit, is not obvious over the cited art. Accordingly, Applicants request removal of this basis of rejection from claims 13, 16-19 and that this basis of rejection not be applied to new claims 31-34.

The Examiner maintains the rejection on the basis that the invention is allegedly obvious over the cited references. Applicants again traverse this rejection, especially for claim 13 as amended, for claims 16 and 18 dependent thereon, and for new claims 31-34. Specifically, the

Examiner has categorized Applicants' earlier arguments as being: (a) arguments that a *prima facie* case of obviousness was not established; (b) arguments that there is not proper motivation to combine teaching; (c) that an analysis of the chronological order teaches against the combination of references; and (d) difficulties taught by the art teach away from a reasonable expectation of success. Applicants will address the Examiner's characterization of each of these arguments as is necessary to demonstrate that the present invention, particularly as amended, is unobvious and therefore patentable over the prior art.

Arguments that a *prima facie* case of obviousness was not established

More specifically, in respect to the arguments regarding establishment of a *prima facie* case of obviousness ((a) above), the Examiner notes that Applicants' arguments against the Examiner's earlier points are characterized as comprising five (5) "prongs." These prongs relate to, among other things, whether the connection between the reference in Khudyakov et al. to Chien constitutes a proper motivation to combine the references (the third prong) and whether Khudyakov et al. suggests that the mosaic protein strategy it teaches could be applied to the present invention (the fourth prong). Applicants would direct the Examiner's attention to these two prongs in more detail as follows.

The third prong.

In support of the Examiner's contention that it is "only the strategies that Khudyakov is trying to distinguish, and not the antigenic sources used to illustrate them," the Examiner refers

to what is characterized as "Khudyakov's constant referral to the utility of mosaic proteins in general, without limiting it to mosaic proteins of HEV." In support of this, the Examiner uses as an example, the last sentence of the abstract, which the Examiner states "suggests that the strategies of both Chien and Khudyakov may be applied equally to HEV and HCV, and any other virus..." Further, the Examiner states that the presentation and comparisons used by the author clearly suggest that the strategy is applicable to Hepatitis subtypes E, C, and B. In response, Applicants submit the Examiner has mischaracterized the teachings of Khudyakov. Specifically, the last sentence of the abstract in reference to the HEV protein produced states "[t]he data obtained strongly indicate a diagnostic potential for the mosaic protein" (emphasis added). This does not constitute a "constant referral to the utility of mosaic proteins in general, without limiting it to mosaic proteins of HEV" as is avowed by the Examiner, but is only a reference to the HEV mosaic. There is no general teaching in this of the applicability of any strategy to anything but HEV. This reference can not then suggest that the strategies of Chien and Khudyakov be applied equally to HEV, HCV or any other virus as this reference by Khudyakov refers specifically only to the mosaic of HEV. Applicants further submit that by interpreting this reference to "the mosaic" by Khudyakov as meaning mosaic proteins that encompass those of the invention, the Examiner must necessarily be relying on inappropriate hindsight. A rejection relying on this inappropriate hindsight is then also necessarily improper. Accordingly, Applicants request its removal and the allowance of claims 13, 16 and 18 to issue.

The fourth prong.

Applicants maintain that the Examiner's earlier statement "Khudyakov et al. further suggest the applicability of the mosaic protein approach for hepatitis viruses other than HEV by teaching successful construction of a mosaic protein for diagnosis of hepatitis B virus" was misguided. Applicants appreciate that the Examiner has indicated at least partial agreement in that Khudyakov et al. suggests that the mosaic protein strategy might be applied to any antigen, but did not necessarily state that it could be applied to hepatitis C virus. However, Applicants disagree with the Examiner that despite this, "when combined, the facts that the mosaic protein approach had already been used with two separate hepatitis virus, the comparison to a second strategy in which HCV had been used and the indication that the strategy taught by either Chien or Khudyakov had broad applicability all suggest that the mosaic approach could be used for HCV" because there is no teaching or suggestion that such a strategy should be used. Indeed, Applicants submit that even the assertion that the strategy taught by either Chien or Khudyakov had broad applicability is at best tenuous. A suggestion, if it exists, that a particular strategy for manipulating proteins can be used to manipulate proteins does not provide the teaching necessary to render the present invention obvious as no such overly general teaching provides the necessary claim limitations as is required for a proper finding of obviousness ("the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP § 2143)). Accordingly, Applicants request removal of this basis of rejection, particularly for claims 13, 16, and 18.

Arguments that there is not proper motivation to combine teaching

While the Examiner has expressed that the argument that Khudyakov did not suggest the application of the mosaic protein strategy to HCV was adequately addressed in the discussion of the "third prong" above, Applicants submit that Examiner's case for the notion that Khudyakov suggests an HCV mosaic is not established.

In regard to the further arguments against the applicability of Khudyakov to HCV, where it is detailed that HEV and HCV are unrelated viruses and that Chien teaches HBV and HCV may require different diagnostic strategies, Applicants submit the Examiner still does not establish a proper basis for the rejection of the claims as obvious. While it is arguably apparent, in hindsight, that the mosaic protein taught can be used to produce diagnostic tools for certain viruses that differ from one another in some manner, this does not indicate that the differences between HEV and HCV structures and infectivity are not relevant to the determination of obviousness. Specifically, the burden to establish obviousness is that the art teaches the invention, not that the art doesn't disprove the possibility of a particular combination. As such, Applicants would rather simply reiterate that the cited art refers to a number of rather different viruses all termed "hepatitis viruses" and that the similarity in their names masks significant difference in their biology. Accordingly, while it is arguably true that, as stated by the Examiner, the "diagnostic strategy taught by Khudyakov may be applied to unrelated viral antigens" (emphasis added), Applicants submit that the art does not establish that it should be so

applied or that one can expect any success if it is so applied. Therefore, Applicants submit that it does not support a finding of obviousness.

Arguments that an analysis of the chronological order teaches against the combination of references

Applicants note the Examiner's position that the "development of new inventions to perform the same or similar function does not make older technology any less obvious to those of ordinary skill in the art, and does not teach away from the prior invention in the sense of rebutting the motivational element of establishing obviousness." However, Applicants continue to maintain that such a chronology does necessarily demonstrate both a long felt need for the product and that, despite the fact that the prior art which supposedly renders the present invention obvious was available for years, others did not satisfy that need using the present invention. Specifically, despite the presence of certain mosaic-like proteins for use in detecting other pathogens and the development of alternative approaches for detecting pathogens (Zhang et al.), the present invention was not attained for years after the teachings of the prior art were available despite an ongoing need for such improved diagnostics. The absence of any such improvements, coupled with the trend within the particular art toward the use of non-mosaic detection systems such as exemplified by Zhang's system, only reinforces the unobvious nature of the present invention as it is a demonstration of "long felt need, but unsolved need" that should properly be considered as one of the secondary considerations (*Graham v. John Deere*,

383 U.S. 1, 148 USPQ 459 (1966)). Applicants, therefore, request that the Examiner does consider this evidence of the present invention non-obviousness.

Arguments that difficulties taught by the art teach away from a reasonable expectation of success

As described by the Examiner, here the Applicants discuss difficulties that one of ordinary skill in the art would face when trying to create an HCV mosaic protein. As noted by the Examiner, this was discussed by the Examiner in discussion of "prong five" of the arguments against a *prima facie* case of obviousness. As also noted by the Examiner, the Examiner characterizes the problems as not being insurmountable. In short, the Examiner maintains that one of skill in the art would have had a reasonable expectation of success despite the difficulties. Furthermore, the Examiner argues that if the Examiner were to accept the Applicants' rationale that the teachings to make mosaic proteins were unpredictable and would, thus, not provide a reasonable expectation of success, the Examiner would be forced to reject the same claims for lack of enablement. This is simply incorrect. The determination of whether there was a reasonable expectation of success for the teaching in the prior art (i.e., in a determination of obviousness) is to be based on what is disclosed in the prior art and on what is known to those of skill in the art. The determination of whether the invention is enabled is properly based on all that was known before (i.e., the prior art) and what is disclosed in the present application. As is clear to the Examiner, the present application includes a method (Restriction Endonuclease Assisted Ligation) that greatly facilitates production of mosaic polypeptides. As is not yet clear

to the Examiner, this method is so fundamentally powerful that it transforms the production of mosaic polypeptides from being a process where there is no reasonable expectation of success to one where there is such an expectation. As such, the conundrum posed by the Examiner that the claims must be either unpatentable on the basis of obviousness or on the basis of lack of enablement is simply invalid.

As is stated in the Office Action, "the specification teaches a technique of making mosaic proteins, a number of homologous NS4 peptides that may be used in the method, and a complete mosaic protein." Applicants concur with the Examiner and therefore submit that the specification as filed does clearly teach the technique. In doing so, it also provides a working example that demonstrates some benefits of the method and mosaic proteins made by the method.

However, Applicants take issue with the Examiner's further characterization that "the real method is [a] method of combining peptides, not of identifying them" and that as a consequence the "applicant has not solved the challenges to any greater degree than any one else skilled in the art." Specifically, the cited prior art teaches generating mosaic proteins by making each separately or by making a gene that expresses each separately. These prior art mosaics could then be tested for effective antigenic reactivity. Failure of a mosaic protein to properly present each antigenic determinant included could not be remedied but by repeating the process of constructing a completely new mosaic. Essentially, the prior art requires undue experimentation

for all but the simplest mosaics (i.e., those with very few different homologous epitopes) as a result of the techniques used to generate or manipulate those mosaics..

The REAL technique taught by the present application solves certain problems relating to production of effective mosaic proteins having a significant number of different homologous epitopes as would be recognized by those of skill in the art. Applicants would direct the Examiner's attention to page 3, line 27 to page 4, line 11, wherein some of the shortcomings of prior art techniques overcome by REAL are taught. In particular, on page 4, lines 3 to 6, the specification teaches that "the use of PCR is disadvantageous in cases where repeated sequences as designed in the gene," as such sequences are recognized by those of skill in the art of not being effectively amplified or replicated with adequate fidelity, or by ETR which "cannot be used to conveniently express short fragments of the synthetic gene." Each of these shortcomings of the prior art are remedied by use of REAL, the technique clearly taught by the specification. Overcoming these shortcomings in the art is instrumental in providing a reasonable expectation of success.

Specifically, reiterative use of the ligation technique to generate a mosaic gene, expression of the encoded mosaic protein, and testing of that mosaic protein for antigenic reactivity as described in the specification allows one of skill in the art to avoid the excessive experimentation necessary using prior art techniques. For example, in making a mosaic antigen comprising many different epitopes using REAL, one of skill in the art could add a further antigen to a mosaic protein already comprising a number of different epitopes and test it for

proper antigenicity. If its antigenic behavior was acceptable, a further antigen could be added by repeating the restriction and ligation process. However, if the antigenic behavior was not acceptable, a slightly or even completely different antigen can be added. Importantly, by being conducted in a controlled stepwise manner, the behavior of antigens being added can be monitored during the process of making the mosaic protein. This greatly reduces the uncertainty that a particular antigen will not be effective in the context of a larger sequence as the process of adding these includes assaying their reactivity. This stepwise addition, as described, is only possible by the removal of original restriction sites between sequences ligated together concomitant with the REAL method. Without removal of the original restriction sites, an attempt to carry-out a stepwise cleavage and ligation to build-up a mosaic would result in all manner of randomly oriented sequences. Without allowing a stepwise addition of sequences to ensure that each sequence included was antigenically reactive and/or didn't interfere with other epitopes, an attempt to build all but the simplest mosaic would have virtually no chance of success (this was, and is, the problem with the prior art in the absence of the REAL method). In short, stepwise construction of mosaic proteins where each step incorporated further epitopes and where the antigenic reactivity of each added epitope can be tested enables the practitioner to make mosaic proteins with ease that otherwise could not be constructed.

In view of this, Applicants submit that the prior art did not provide a reasonable expectation of success of mosaic proteins with the characteristics as claimed and that the present

specification does provide a reasonable expectation of success. Accordingly, Applicants submit that claims 13, 16 and 18 are unobvious and are fully-enabled.

B. Claims 13, 16 and 18 are also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Valenzuela et al., U.S. Patent Number 6,428,792. Specifically, the '792 patent allegedly describes a multiple copy fusion antigen and expression vectors encoding the protein wherein the protein includes at least two copies of a given epitope and wherein a copy is defined to include equivalent antigenic determinant from different strains of the same virus. However, as is discussed by the Examiner, "the protein taught by the reference is required to contain at least two non-homologous/non-adjacent epitopes (col. 7, lines 50-55)." Thus, Claim 13 does not, as is implicitly acknowledged by the Examiner, correspond to what is actually taught by the '792 patent. Nonetheless, the Examiner maintains that one of skill in the art would be both motivated and have a reasonable expectation of success in making the proteins and nucleic acids encoding them from the teachings of the patent.

Applicants submit that this is inadequate for a proper finding of obviousness. Specifically, as is noted by the Examiner, the protein taught by Valenzuela does not teach the protein as claimed. That is to say, Valenzuela does not teach each limitation of the claimed invention. As such, even the basic considerations which apply to obviousness rejections are not fully met. In particular, as is noted in the MPEP § 2141, "[w]hen applying 35 U.S.C. 103, the following tenets of patent law must be adhered to: (A) [t]he claimed invention must be

considered as a whole" (emphasis added) (*Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed Cir. 1986)). By the Examiner's admission, each and every limitation of the claimed invention is not taught by Valenzuela. As outlined above, this is not adequate for a proper finding of obviousness. Applicants therefore respectfully request removal of this basis of rejection and allowance of claims 13, 16 and 18 to issuance.

V. New claims 31-34 are patentable

Newly added claims 31-34 are directed to nucleic acids encoding mosaic proteins of the present invention. These claims parallel claims 1 and 5-7 in issued U.S. patent number 6,030,771 which issued from Application Serial No. 09/921,887, the direct parent of the present application (the present application is a divisional of Application Serial No. 09/921,887), but are directed to nucleic acids encoding mosaic proteins rather than the mosaic proteins themselves. New claims 31 and 34 deviate slightly in wording from the corresponding claims in the issued patent in that they recite "more than two" rather than "at least three," but Applicants submit that there is no difference between the two in meaning or scope.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Credit Card Payment Form PTO-2038 is enclosed authorizing payment in the amount of $1098.00 ($168.00 for two (2) new independent claims in excess of three and $930.00 for a three (3) month extension of time). This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required or to credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Gwendolyn D. Spratt
Registration No. 36,016

Customer Number 23859
(404) 688-9880 (Fax)
(404) 688-0770 (Tel)

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8

I hereby certify that this correspondence, and any items attached hereto, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Gwendolyn D. Spratt

6-3-03
Date

Version of claims with markings to show changes made

13. (Thrice amended) A nucleic acid encoding a protein comprising more than two homologous antigenic peptides from the same domain from different genotypes of hepatitis C virus.

17. (Amended) [The nucleic acid of claim 16,] A nucleic acid encoding a protein comprising more than two antigenic peptides from the same domain from different genotypes of hepatitis C virus and wherein the mosaic protein comprises the amino acid sequences set forth in SEQ ID NOs:23-33.

19. (Amended) [The nucleic acid of Claim 18,] A nucleic acid encoding a protein comprising more than two antigenic peptides from the same domain from different genotypes of hepatitis C virus, wherein the antigenic peptides are from non-structural proteins, and wherein the mosaic protein comprises the amino acid sequence set forth in SEQ ID NO:52.